

# Picotamide reduced all-cause mortality more than aspirin in type 2 diabetes mellitus and peripheral arterial disease

Neri Sernerri GG, Coccheri S, Marubini E, Violi F. **Picotamide, a combined inhibitor of thromboxane A<sub>2</sub> synthase and receptor, reduces 2-year mortality in diabetics with peripheral arterial disease: the DAVID study.** *Eur Heart J.* 2004;25:1845-52.

## QUESTION

In patients with type 2 diabetes mellitus and peripheral arterial disease (PAD), is picotamide better than aspirin for preventing all-cause mortality and major cardiovascular (CV) events?

## METHODS

**Design:** Randomized placebo-controlled trial (Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics [DAVID]).

**Allocation:** Concealed.\*

**Blinding:** Blinded (clinicians, patients, data collectors, outcome assessors, and data safety and monitoring committee).\*

**Follow-up period:** 24 months.

**Setting:** 86 centers in Italy.

**Patients:** 1209 patients who were 40 to 75 years of age (mean age 64, 73% men) with type 2 diabetes for  $\geq 5$  years and PAD ( $\geq 2$  of intermittent claudication for  $> 2$  mo, loss of posterior tibial pulse in the foot, ankle–arm pressure ratio  $< 0.90$  or  $> 1.30$  in the posterior or anterior tibial artery of the foot, amputation or reconstructive surgery in patients with previous intermittent claudication, or angioplasty). Exclusion criteria included myocardial infarction (MI), stroke, or unstable angina in the previous 6 months; severe neurologic or mental deficits; severe comorbid conditions that would limit life

expectancy to  $< 2$  years; serum creatinine  $> 2.0$  mg/dL (176  $\mu$ mol/L); pregnancy; severe uncontrolled hypertension; active peptic ulcer or gastrointestinal bleeding in the previous 6 months; total cholesterol level  $\geq 300$  mg/dL (7.69 mmol/L); and scheduled major surgery that would require long-term use of anticoagulants.

**Intervention:** Twice-daily picotamide, 600 mg ( $n = 603$ ), or aspirin, 320 mg in the morning and a placebo tablet in the evening ( $n = 606$ ).

**Outcomes:** All-cause mortality. Secondary outcomes were the composite endpoint of death and nonfatal CV events (MI, ischemic stroke [acute neurologic vascular event with focal signs for  $\geq 24$  h and a CT scan–ecognized ischemic lesion without evidence of intracranial hemorrhage], or major amputation [above the ankle, not because of trauma or cancer]), and adverse events.

**Patient follow-up:** 95% (intention-to-treat analysis).

## MAIN RESULTS

Fewer patients who received picotamide died than did those who received aspirin (Table). The groups did not differ for the composite endpoint of mortality plus nonfatal CV events (Table). Picotamide was associated with fewer gastrointestinal adverse events than aspirin (10.9% vs 18.3%,  $P < 0.001$ ). The groups did not differ for other adverse events.

## CONCLUSIONS

In patients with type 2 diabetes mellitus and peripheral arterial disease, picotamide was more effective than aspirin for preventing all-cause mortality. Picotamide did not reduce nonfatal cardiovascular events.

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\*See Glossary.

### Picotamide vs aspirin for type 2 diabetes mellitus and peripheral arterial disease at 24 months†

Outcomes	Picotamide	Aspirin	RRR (95% CI)	NNT (CI)
All-cause mortality	2.8%	5.1%	45% (2 to 69)	44 (22 to 1025)
Composite endpoint	7.5%	9.0%	16% (–22 to 43)	Not significant

†Composite endpoint = death and nonfatal cardiovascular events (myocardial infarction, ischemic stroke, and major amputation). Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

## COMMENTARY

Patients with type 2 diabetes have increased platelet adhesiveness (1). As a result, aggressive antiplatelet therapy would be expected to improve CV outcomes. However, 2 recent publications have shown that while aspirin improved CV outcomes in nondiabetic patients, this was not the case in patients with diabetes (2, 3).

Aspirin inhibits platelet cyclooxygenase activity, leading to a decrease in thromboxane A<sub>2</sub> (a potent platelet activator), while simultaneously decreasing the production of prostacyclin (a mediator known to decrease platelet aggregation and to produce vasodilation). The reduced benefit of aspirin in patients with diabetes is thought to occur because the loss of thromboxane A<sub>2</sub> is minimized by the presence of numerous other platelet activators/aggregators present in the diabetic state. Thus, the platelet remains activated/aggregable while having lost the anti-aggregating influence of prostacyclin. As a result, specific thromboxane A<sub>2</sub> blockers have been developed to provide antithromboxane benefits, which do not lower prostacyclin levels.

The 24-month DAVID study by Neri Sernerri and colleagues compared picotamide with daily aspirin in patients with type 2 diabetes and PAD, and showed a decreased risk for all-cause mortality. The only disappointing finding was the nonsignificant reduction of the composite

endpoint of mortality and nonfatal CV events. This leaves the interpretation difficult and a need for further confirmatory trials.

If proven equivalent to or better than aspirin in CV prevention, picotamide (which causes less bleeding requiring hospitalization and a lower frequency of gastrointestinal discomfort than aspirin) will be a welcome addition to calm the hyperactive platelets in diabetic patients. As we wait, the current recommendation by the American Diabetes Association of the use of daily aspirin (75 to 162 mg) in diabetic patients with vascular disease, age  $> 40$  years, or with additional CV risk factors, should be followed (4).

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## References

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